

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

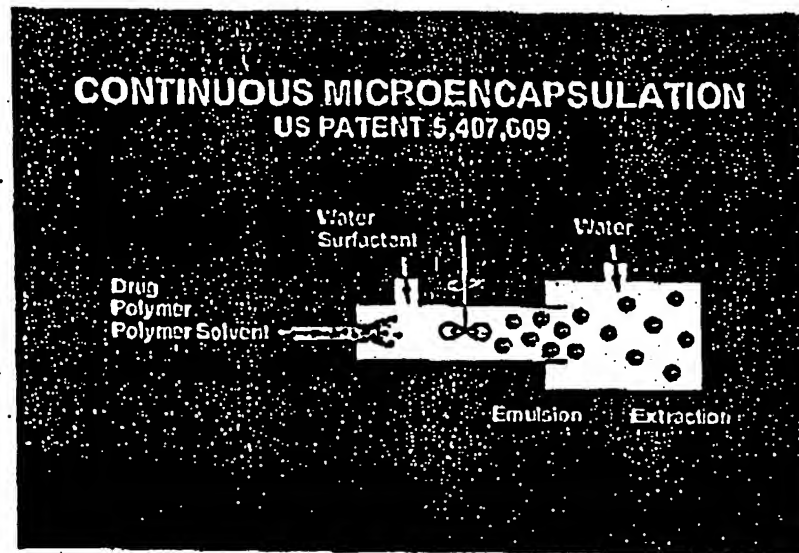
Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Problem Image Mailbox.**

## SOUTHERN RESEARCH'S PATENTED MICROENCAPSULATION PROCESS



### Advantages

- US Patent issued 1995
- Fast encapsulation time -- milliseconds
- Minimal exposure to polymer solvent
- High encapsulation efficiency
- Good Yields
- Makes small microparticles  
    <100 micron   <10 micron

### Drugs Microencapsulated

- Proteins
- Peptides
- Small molecules
- Water-soluble drugs
- Hydrophobic drugs
- Drugs encapsulated in  
    lactide/glycolide polymers

FIGURE 1

FIGURE 2

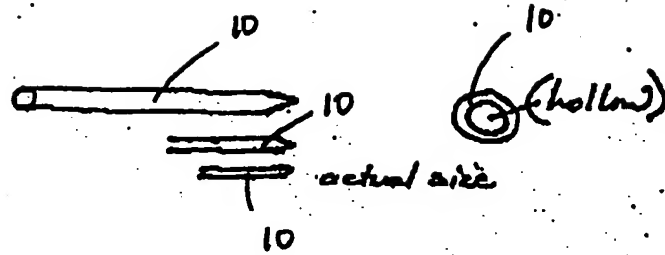
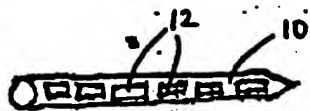
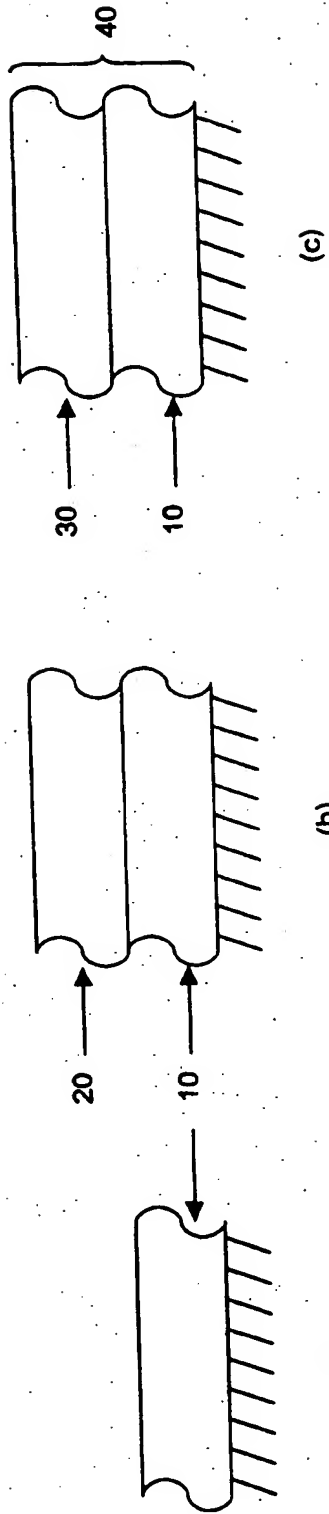


FIGURE 3



**FIGURE 4**

## Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Hardness:	F	B	3B	4B	F


## Conditions: 5 minutes in 37°C pH 7.4 Saline Buffer

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Hardness:	F	B	9B	<9B	F

Hardness Rating:

2H-H-F-HB-B-2B-3B-4B-5B-6B-7B-8B-9B

Harder



Softer

FIGURE 5

## Conditions: Ambient

<b>Material:</b>	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
<b>Resistance To Cracking</b>	< 3 mm	< 3 mm	< 3mm	< 3mm	<3mm

## Conditions: 5 minutes in 37°C pH 7.4 Saline Buffer

<b>Material:</b>	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
<b>Resistance To Cracking</b>	< 3 mm	< 3 mm	< 3mm	< 3mm	< 3mm

**FIGURE 6**

Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Class:	5B	5B	5B	4B	5B

Class Rating: 5B = 0% of coating removed from substrate  
 4B = Less than 5% of coating removed from substrate

**FIGURE 7**

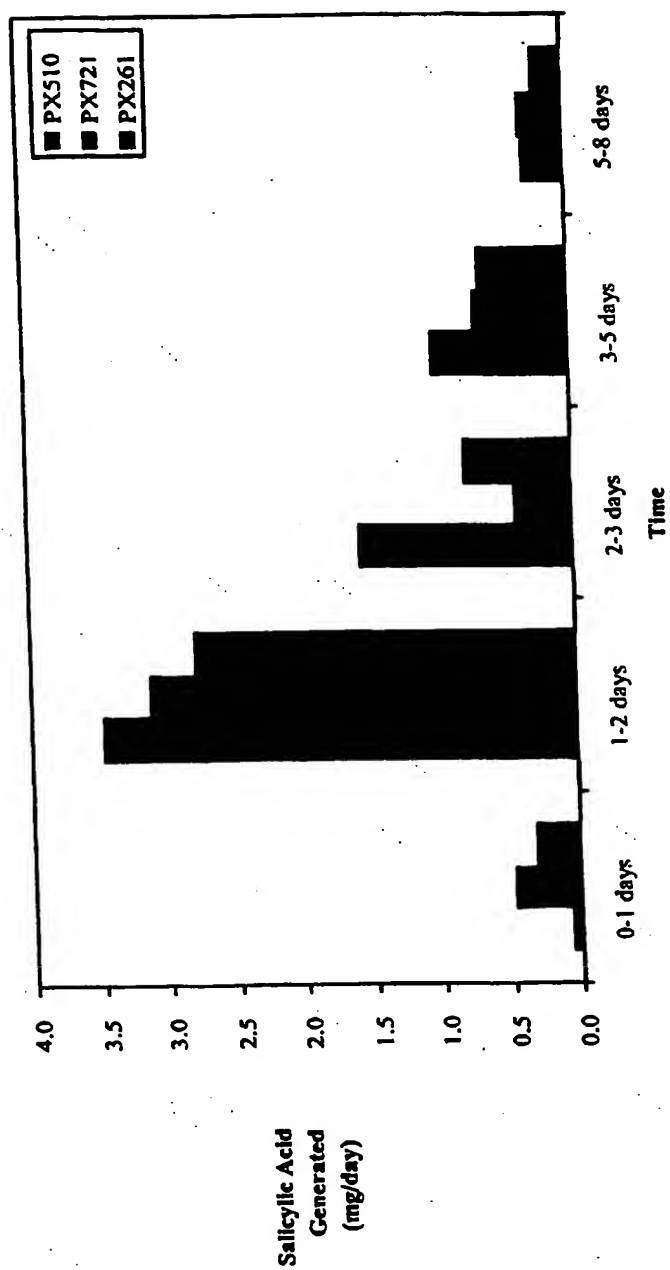


FIGURE 8A



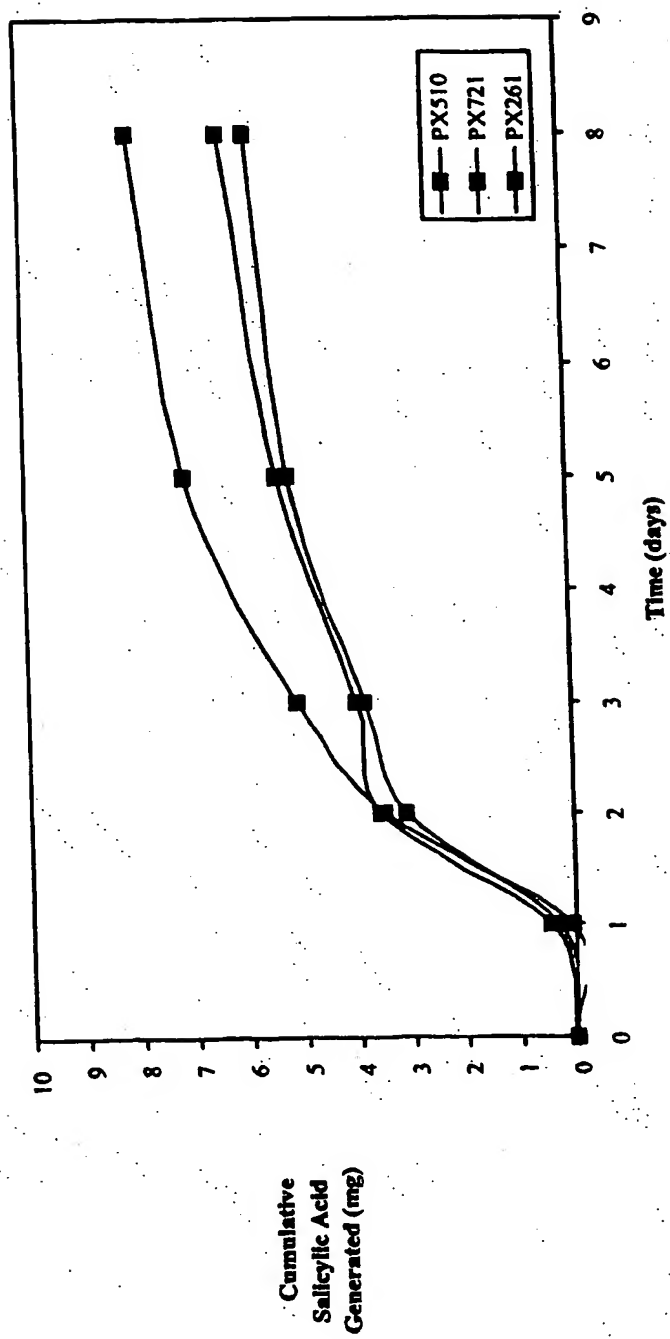


FIGURE 8B

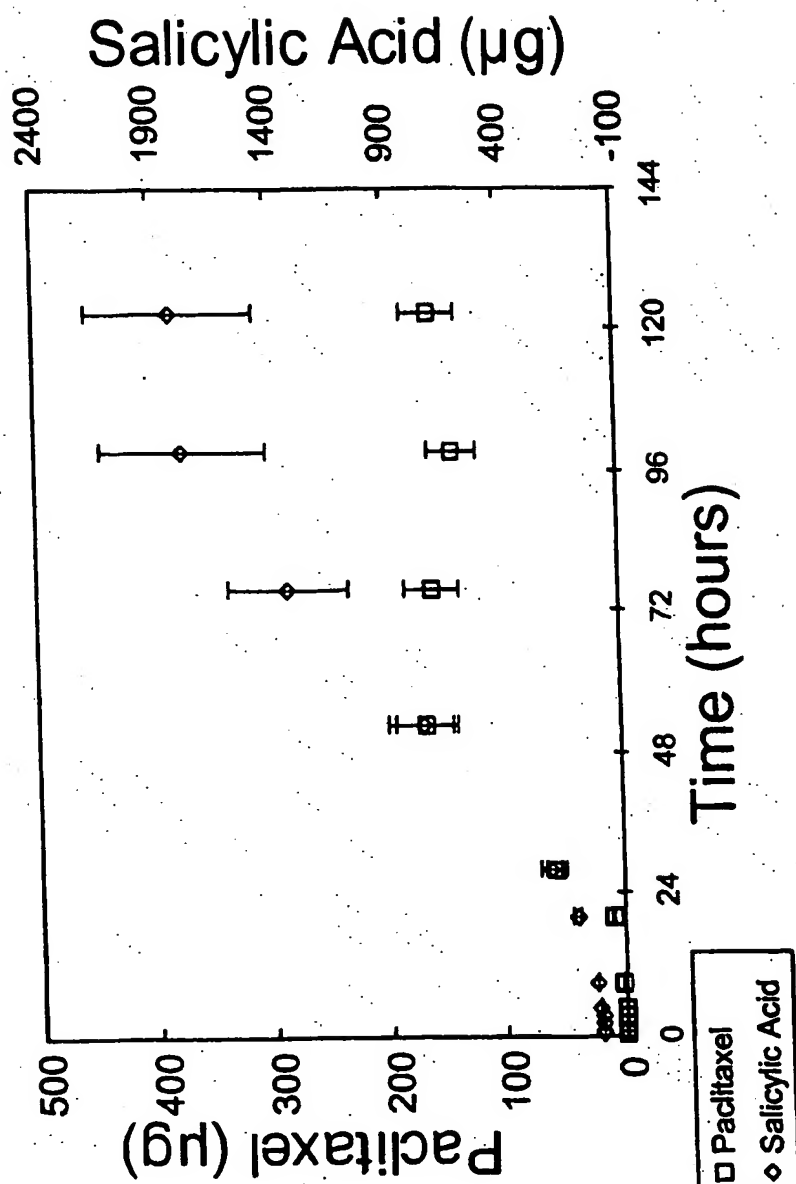


FIGURE 9A

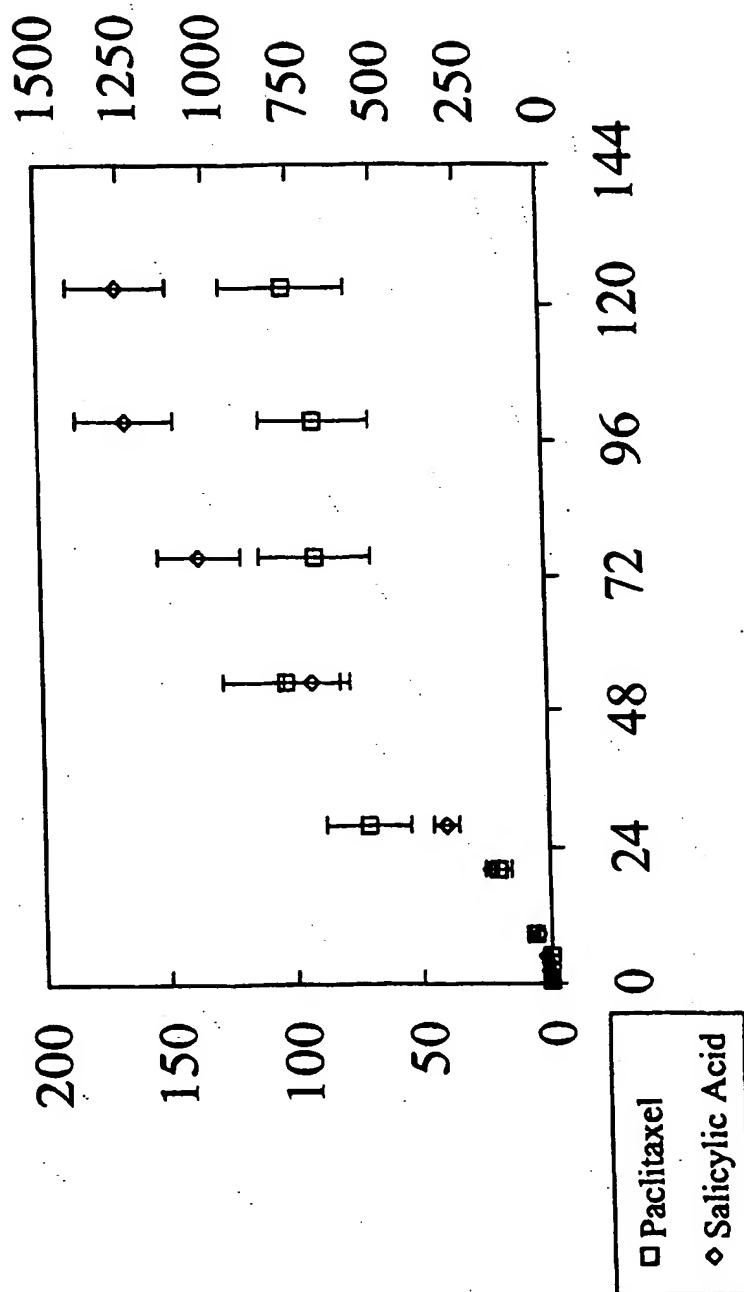
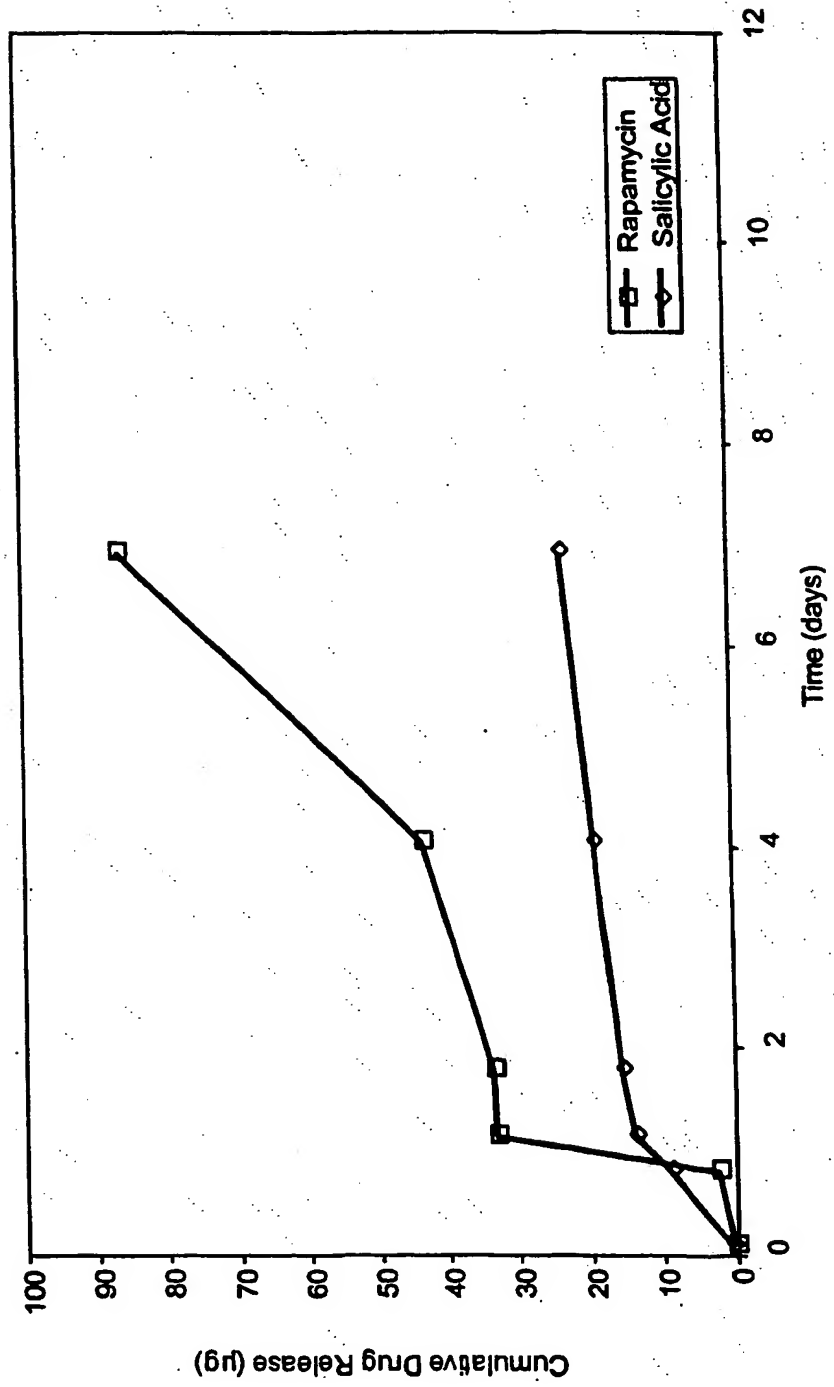


FIGURE 9B

## Formulation

Property	PX510	PX721	PX261	PX749
$T_g$ ( C )	44	38	29	16
Tensile modulus (MPa)	2.0 (25 C) 5.1 (37 C)			3.0 (25 C)
Yield Strength (MPa)	Not observed			6.0 (25 C)
Ultimate Elongation (%)	1.5 (25 C) 350 (37 C)			500 (25 C)

**FIGURE 10**

**FIGURE 11**

E Beam (3 MRad)		$\gamma$ (25-35 KGys)			
Property	PX510	PX721	PX261	PX510	PX721 PX261
MW	-28%	-39%	-26%	-14%	N/C N/C
Hardness	-2 units	N/C	-1 unit	N/C	-3 units -2 units
Flexibility	N/C	N/C	N/C	N/C	N/C N/C
Adhesion	N/C	N/C	-1 unit	N/C	N/C N/C

N/C: no change

FIGURE 12

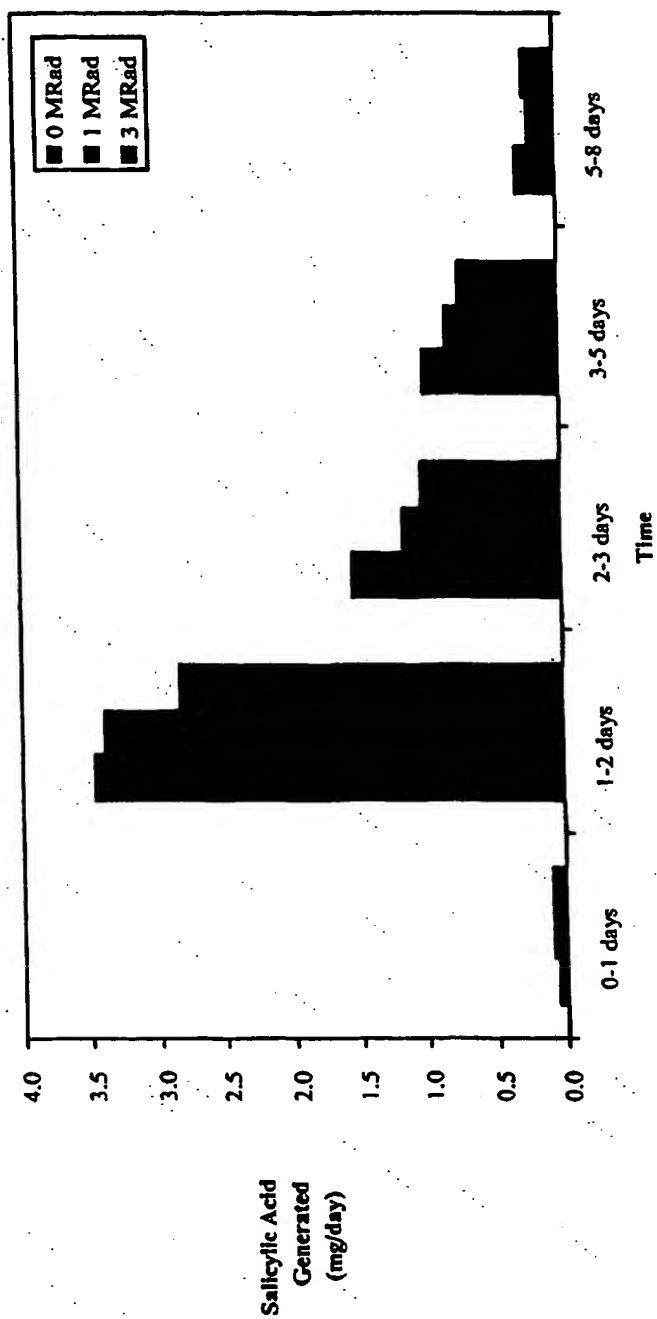
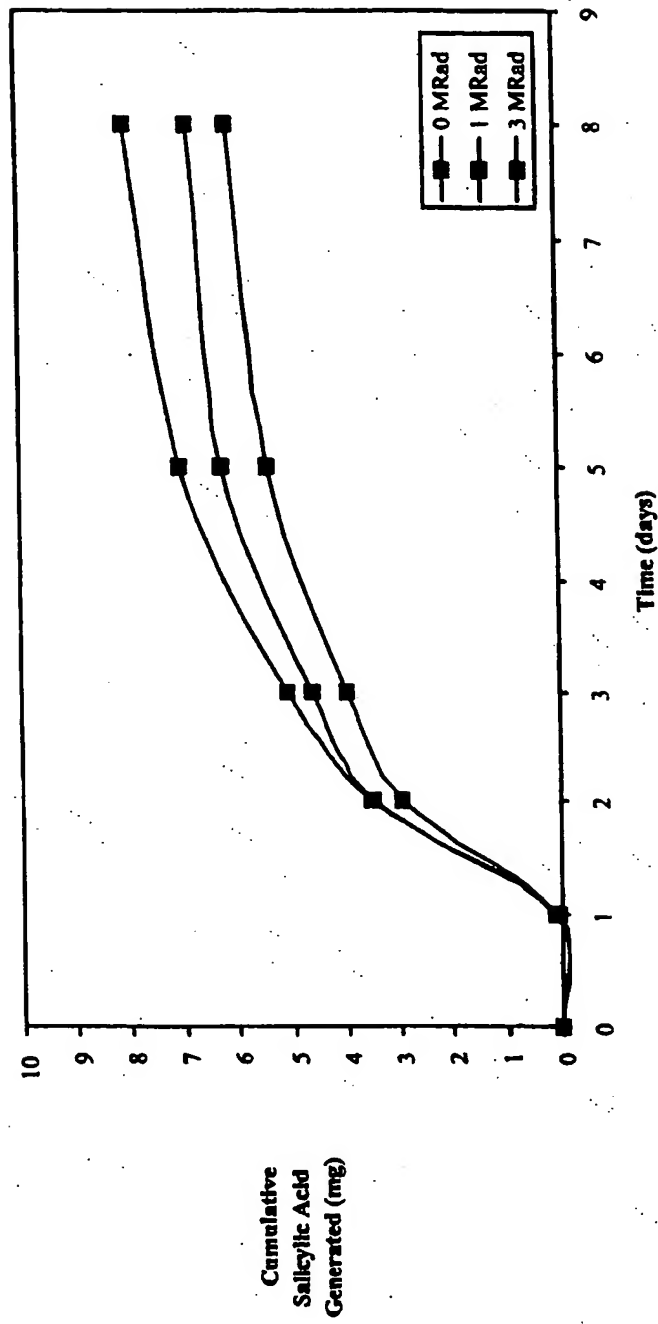


FIGURE 13A

**FIGURE 13B**



# PX242 20-53 Coated Coupon Diflunisal Elution

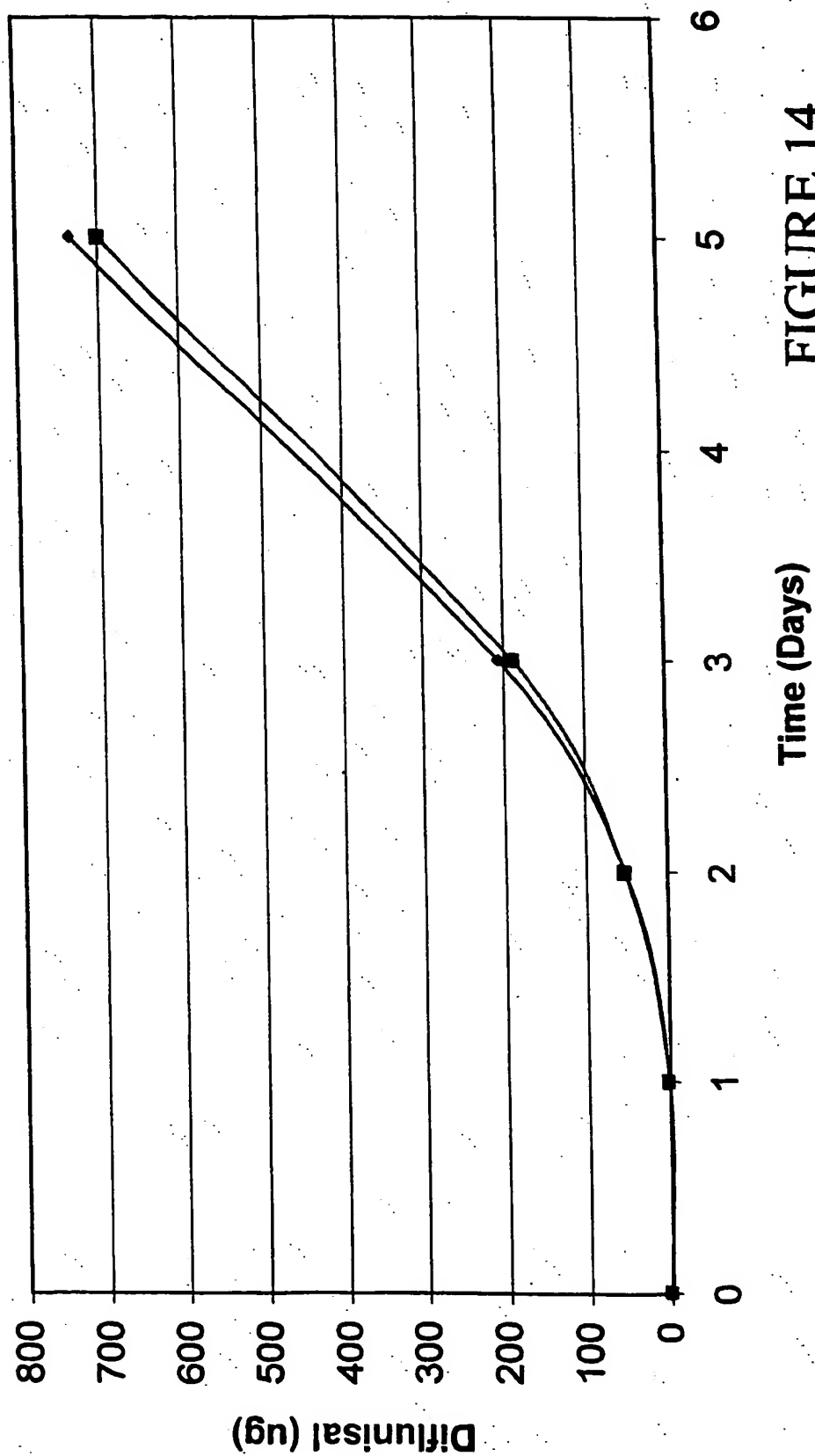


FIGURE 14

# PX242 20-53 Coated Coupon Diflunisal Elution

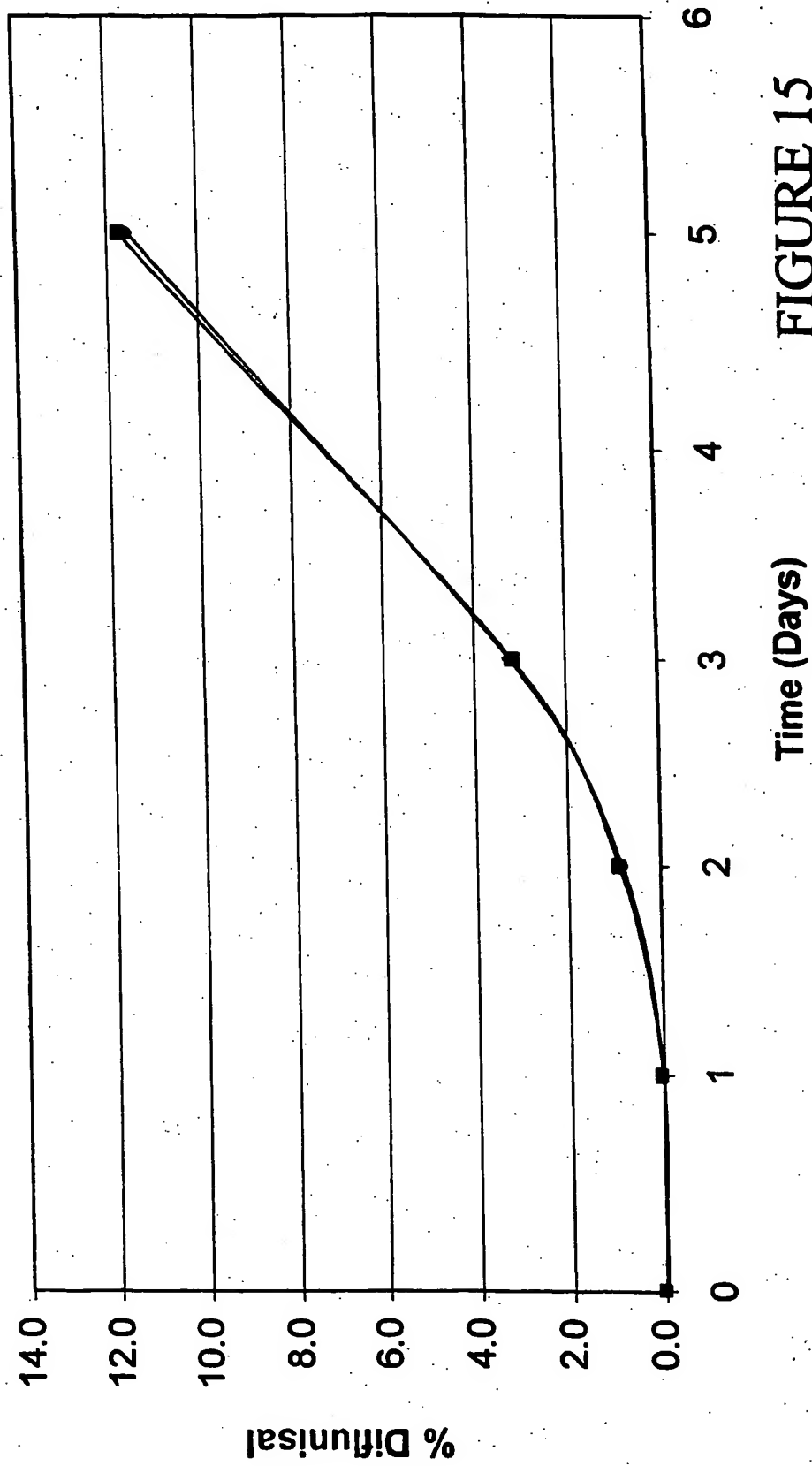
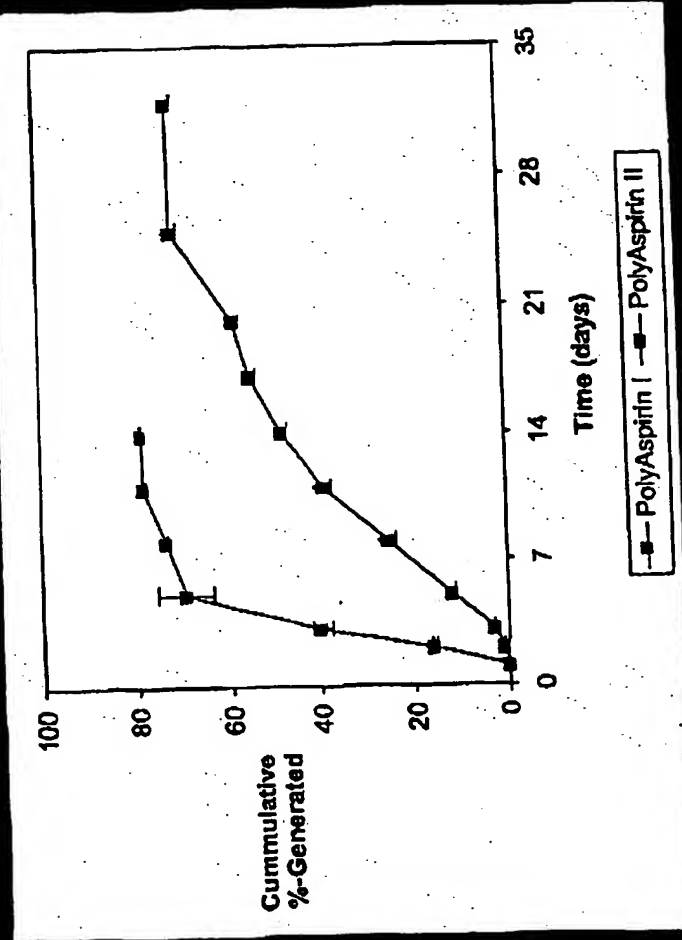


FIGURE 15

# Erosion of PolyAspirin I & II

Generation of NSAID into 37 °C pH 7.4 PBS from  
~5  $\mu\text{m}$ -thick Coatings on 316L SS Plates



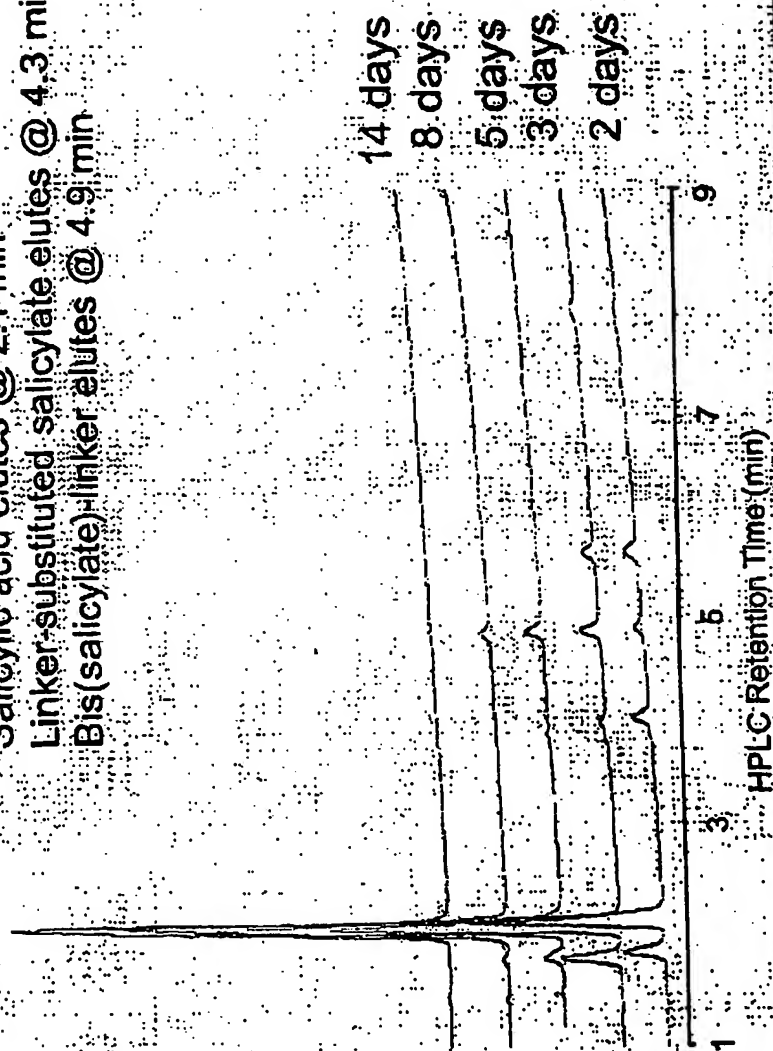
CONFIDENTIAL

FIG. 16

NOVARTIS  
CORPORATION

# Erosion Profile for PolyAspirin I

Salicylic acid elutes @ 2.1 min  
Linker-substituted salicylate elutes @ 4.3 min  
Bis(salicylate)-linker elutes @ 4.9 min



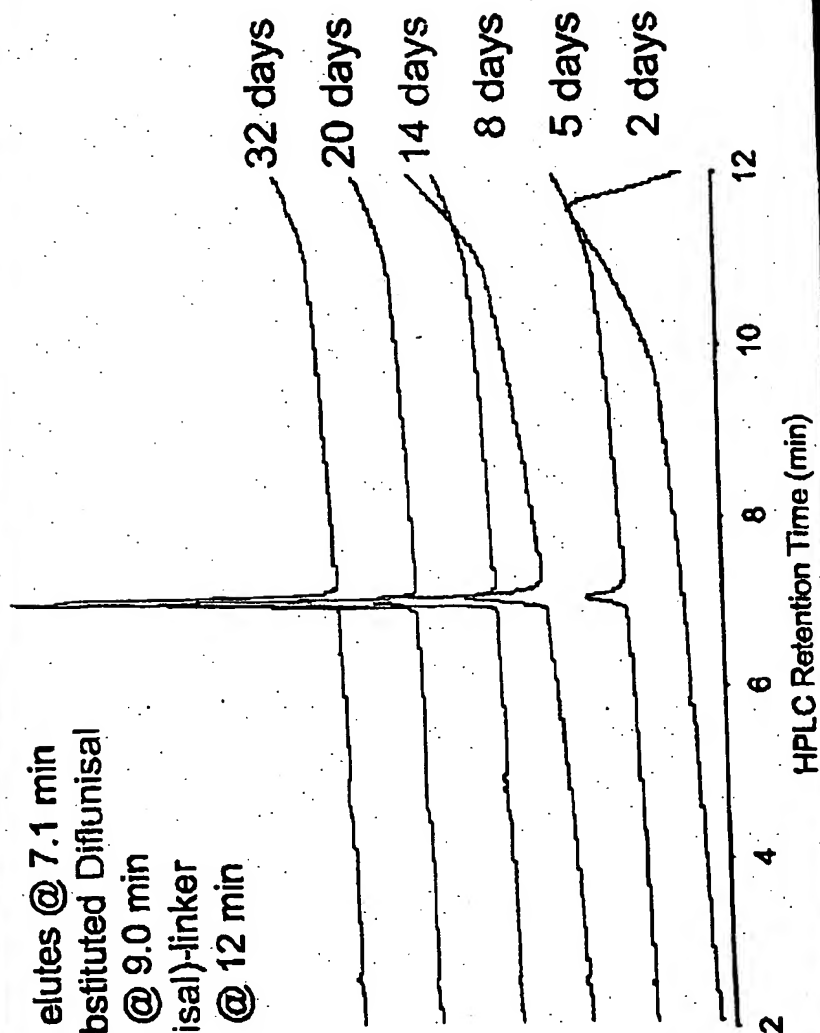
CONFIDENTIAL

FIG. 17

CORPORATION

# Erosion Profile for PolyAspirin II

Diflunisal elutes @ 7.1 min  
Linker-substituted Diflunisal  
elutes @ 9.0 min  
Bis(diflunisal)-linker  
elutes @ 12 min



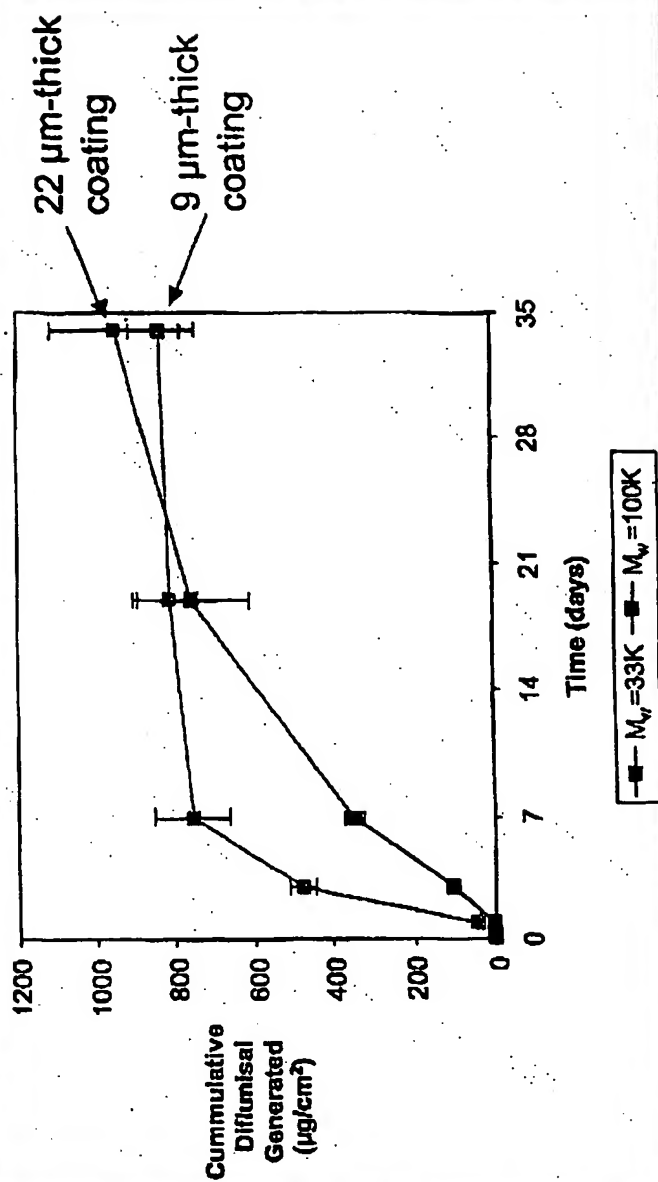
CONFIDENTIAL

CORPORATION

FIG. 18

# Effect of MW on Erosion

Generation of Diflunisal from PolyAspirin II into  
37 °C Serum from Coatings on 316L SS Plates

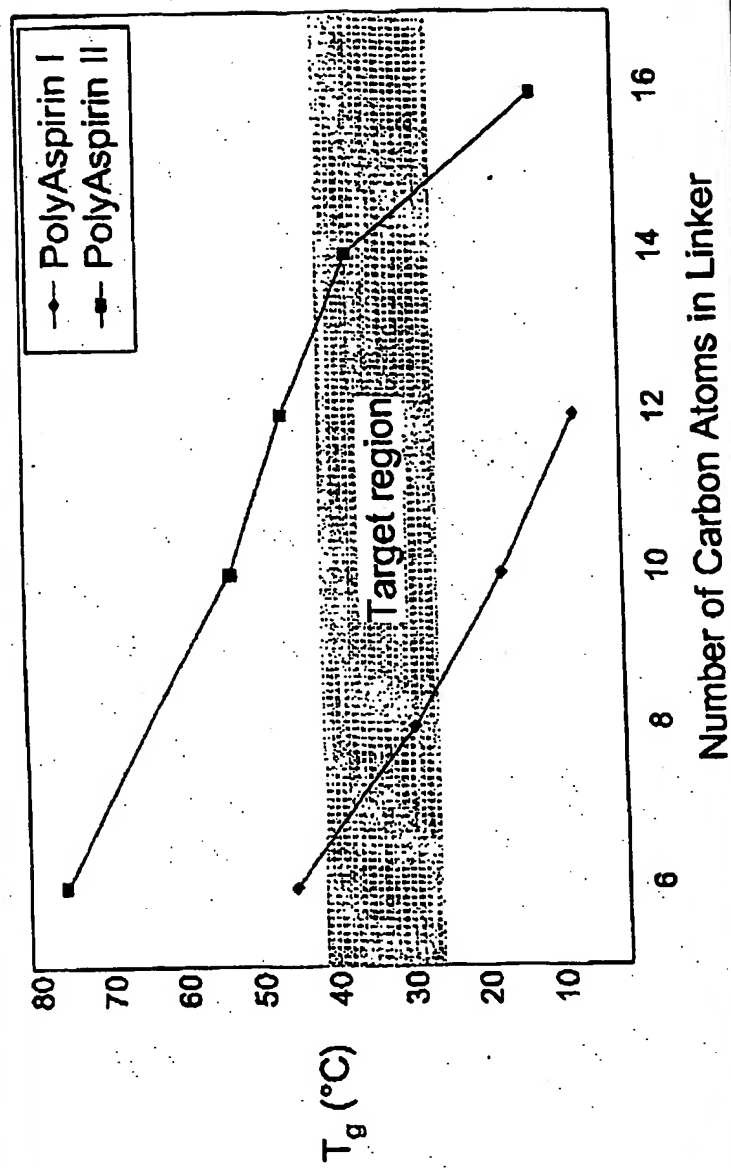


CONFIDENTIAL

FIG. 19

CORPORATION

# Tuning Mechanical Properties



CONFIDENTIAL

FIG. 20

CORPORATION

# Thermoanalysis of PolyAspirin™

Property	PolyAspirin I	PolyAspirin II	
	PX261 $M_w \sim 20K$	PX657 $M_w \sim 33K$	$M_w \sim 100K$
$T_g$ (°C)	29	36	44
Ultimate Stress (kPa)	1700 (25°C) >2000 (37°C)	>2800 (25°C)	>2600 (25°C)
Ultimate Elongation (%)	>500 (25°C) >500 (37°C)	>4 (25°C)	>500 (25°C)
Toughness (kPa)	>3900 (25°C) >4400 (37°C)	>560 (25°C)	>4000 (25°C)



CONFIDENTIAL

FIG. 21



# Properties of PolyAspirin™ Coatings

## PolyAspirin I      PolyAspirin II

PX261      PX657  
 $M_w \sim 20K$        $M_w \sim 33K$        $M_w \sim 100K$

### Test

#### Hardness

Ambient

5 min in PBS, 37 °C  
 1 hr in PBS, 37 °C

F      3H  
 2B      B  
 8B      4B

#### Flexibility

Ambient

5 min in PBS, 37 °C  
 1 hr in PBS, 37 °C

<3 mm      <3 mm  
 <3 mm      <3 mm  
 <3 mm      <3 mm

#### Adhesion

Ambient

5B      5B

PolyAspirin  
 CORPORATION

CONFIDENTIAL

FIG. 22

# PolyAspirin Coatings with Admixtures

## PolyAspirin II (PX657)

Test      No Admixture      20% Paclitaxel Admixed

<u>Hardness</u>		
Ambient	F	F
5 min in PBS, 37 °C	2B	F
1 hr in PBS, 37 °C	8B	6B
<u>Flexibility</u>		
Ambient	<3 mm	<3 mm
5 min in PBS, 37 °C	<3 mm	<3 mm
1 hr in PBS, 37 °C	<3 mm	<3 mm
<u>Adhesion</u>		
Ambient	5B	5B

CONFIDENTIAL

FIG. 23

# Erosion of PolyAspirin I & II

Diflunisal Generation & Paclitaxel Release into 37 °C Serum from ~5  $\mu\text{m}$ -thick Coatings on 316L SS Plates

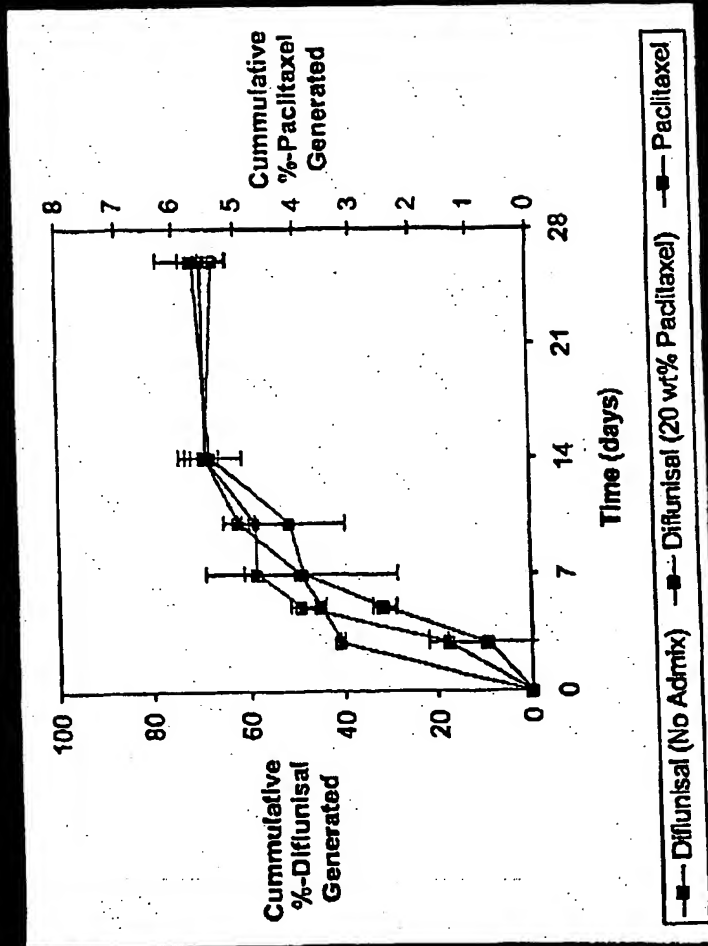


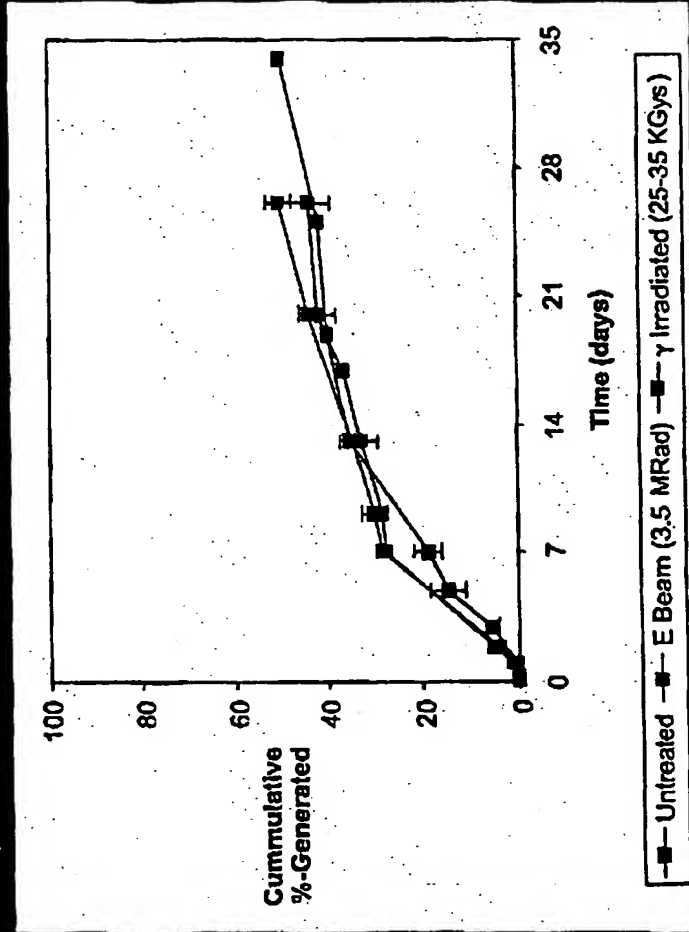
FIG. 24

CONFIDENTIAL

NO. 3410000  
CORPORATION

# Erosion of Sterilized PolyAspirin II

Generation of Diflunisal into 37 °C Serum from  
~5 µm-thick Coatings on 316L SS Plates



CONFIDENTIAL

FIG. 25

3M  
CORPORATION

# $\gamma$ Irradiation (25-35 Kgys)

## PolyAspirin I      PolyAspirin II

PX261      PX657  
 $M_w \sim 20K$        $M_w \sim 100K$

Property

MW

N/C

-50%

Hardness

-2 units

-3 units

Flexibility

N/C

.

Adhesion

N/C

.

N/C: no change

CONYMECH  
 CORPORATION

CONFIDENTIAL

FIG. 26

# E Beam (3-4.5 MRad)

## PolyAspirin I      PolyAspirin II

Property	PX261 $M_w \sim 20\text{ K}$	PX657 $M_w \sim 33\text{ K}$ $M_w \sim 80\text{ K}$
----------	---------------------------------	--

MW

-26%

+5%

-30%

Hardness

-1 unit

+2 units

N/C

Flexibility

N/C

-

N/C

Adhesion

-1 unit

-

N/C: no change

CONFIDENTIAL

FIG. 27

# Kinetics of NSAID Generation

30/39

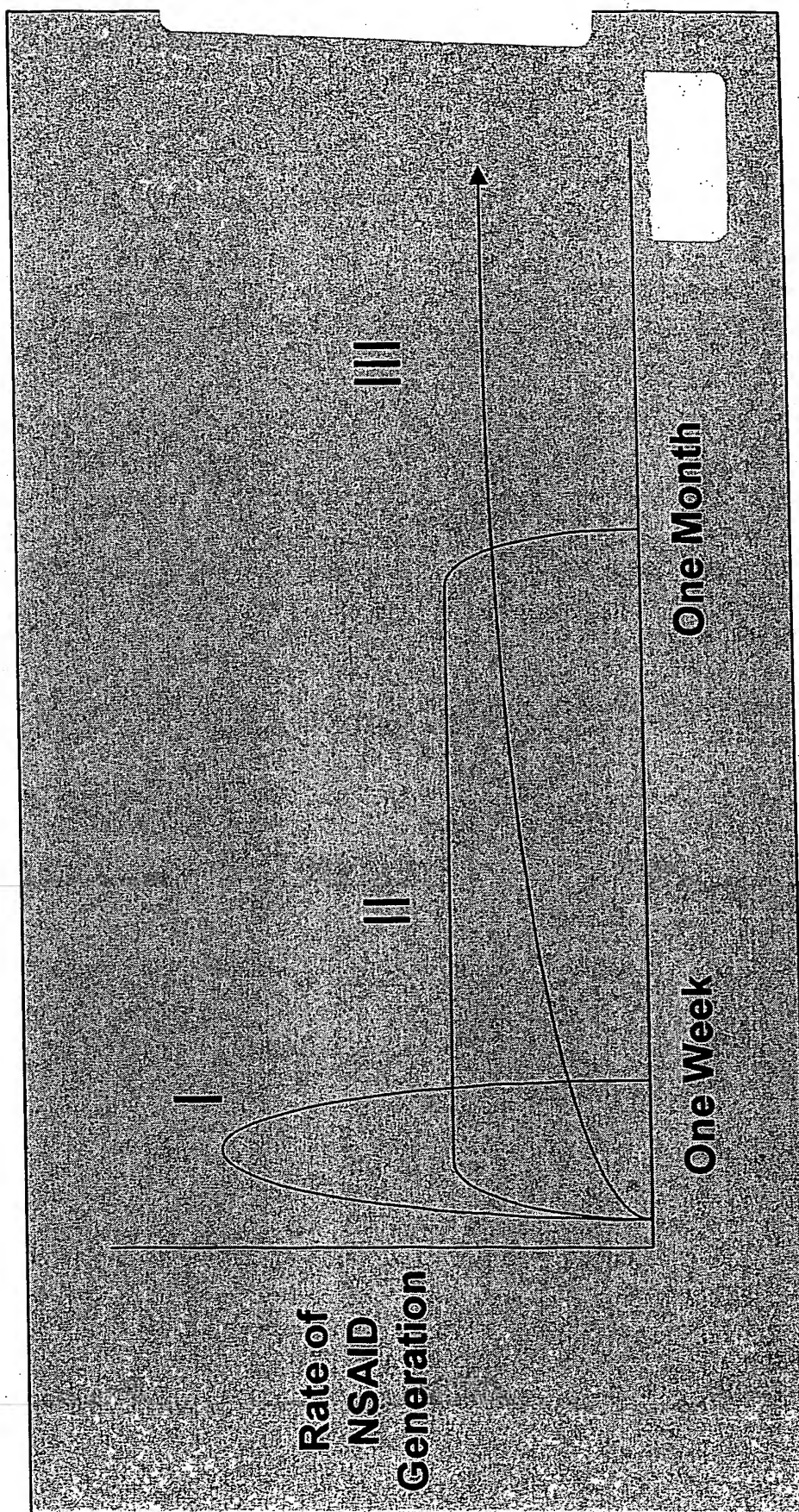
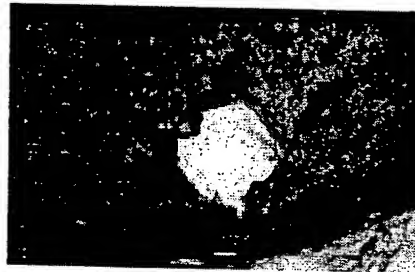
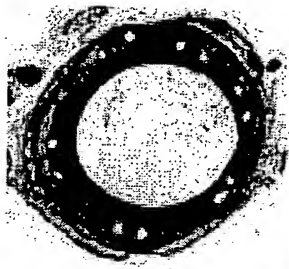
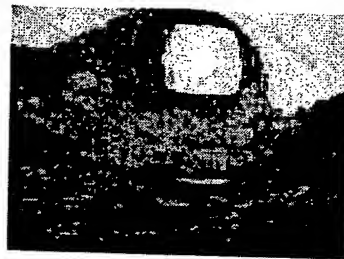
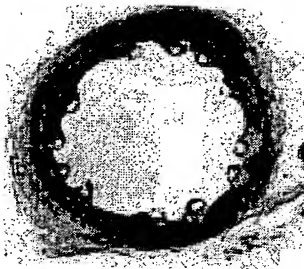


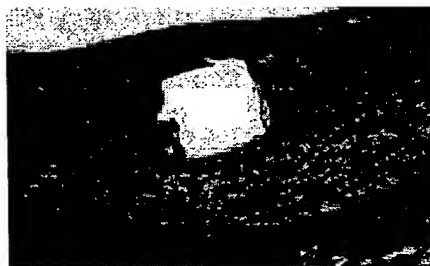
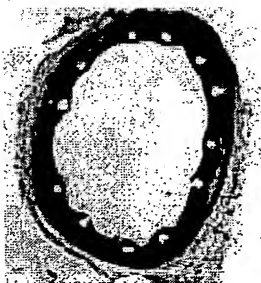
FIG. 28



**FIG. 29**



**FIG. 30**



**FIG. 31**



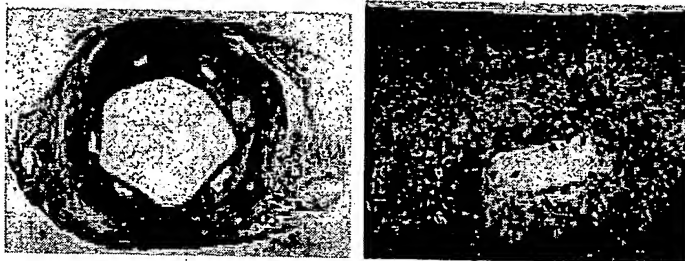


FIG. 32



FIG. 33

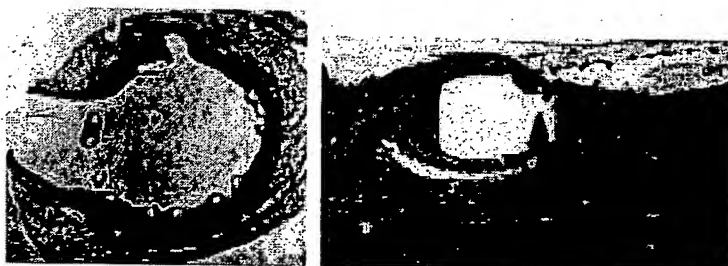
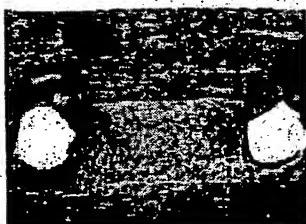


FIG. 34



**FIG. 35**



**FIG. 36**

FIG. 37

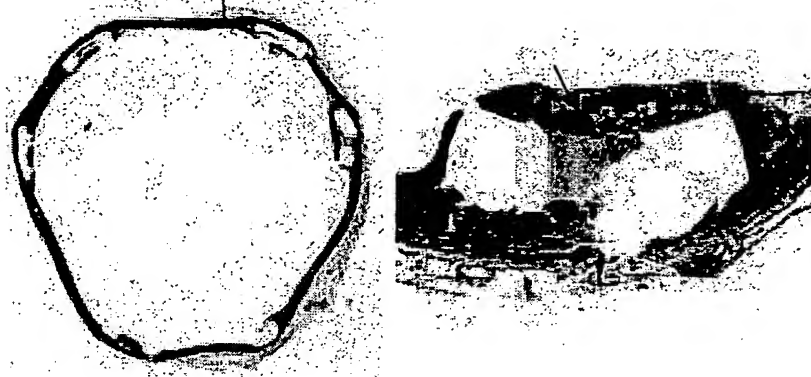


FIG. 38

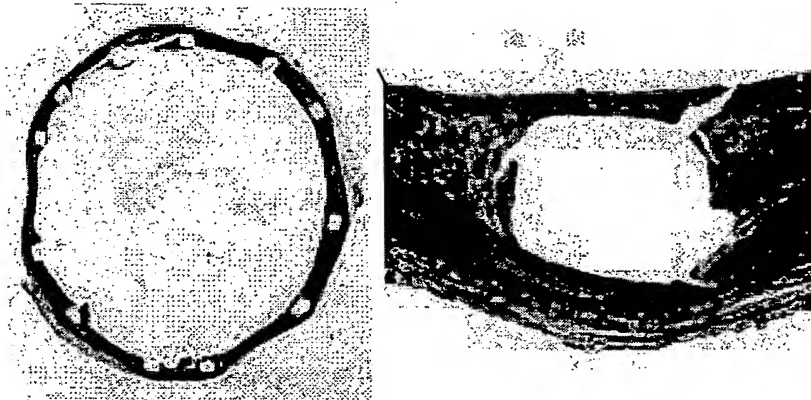
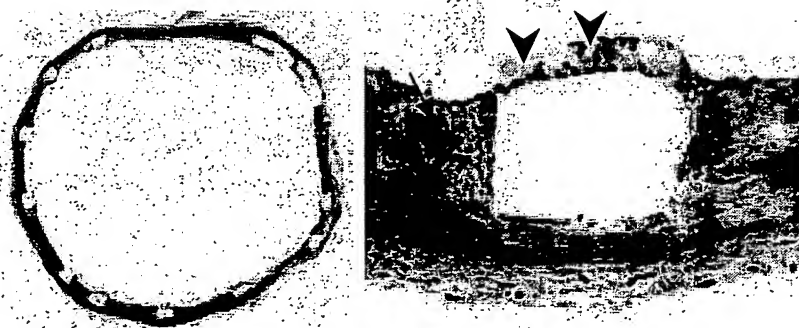
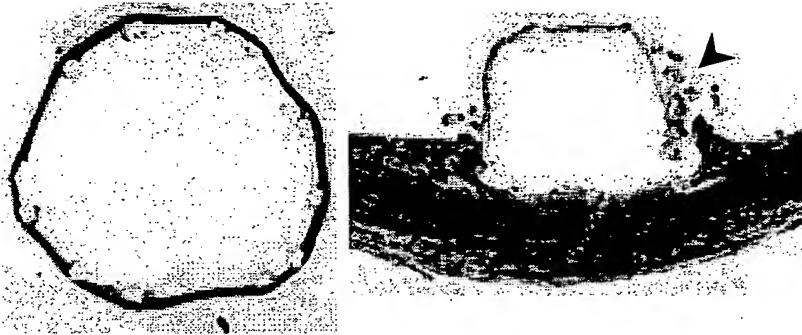
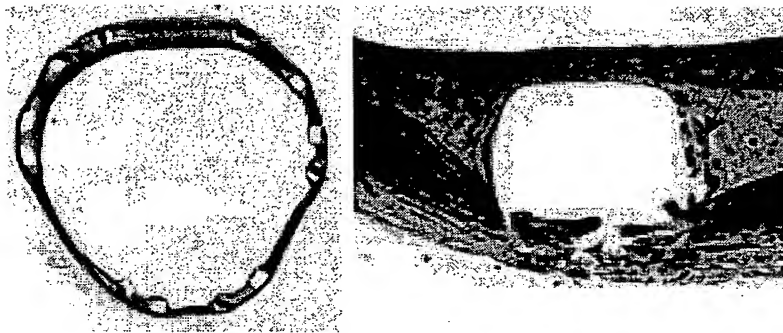


FIG. 39

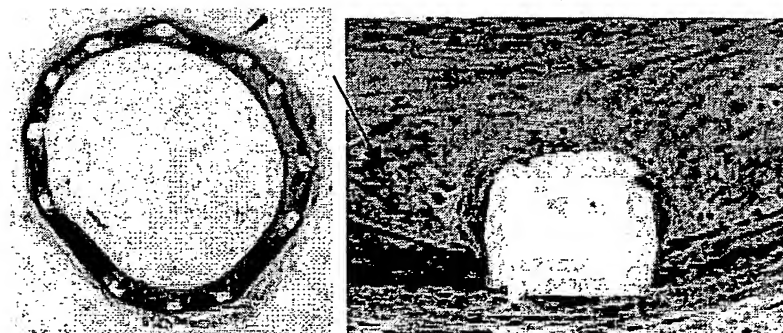




**FIG. 40**



**FIG. 41**



**FIG. 42**

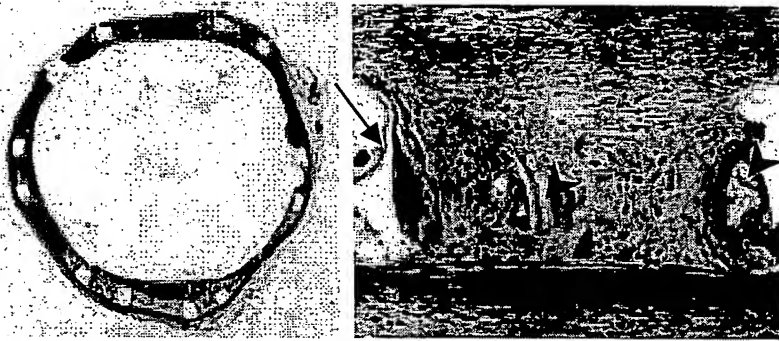
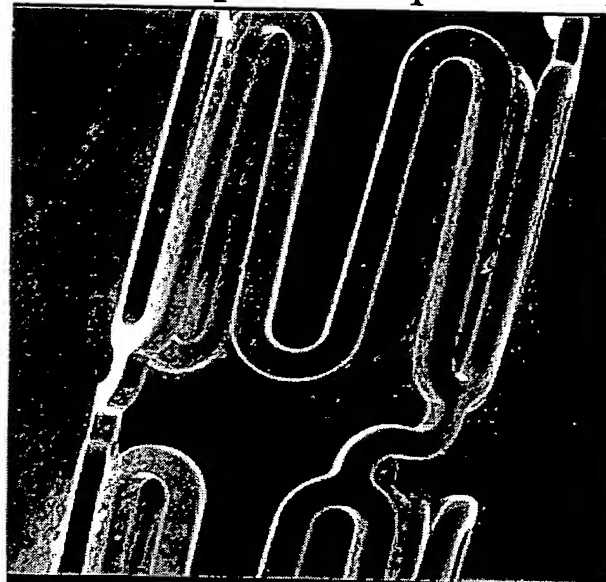


FIG. 43

uncrimped/unexpanded



15.0 kV 1mm AMRAY

FIG. 44a



23.0X 15.0 kV 100µm AMRAY #0000

FIG. 44b

uncrimped/unexpanded

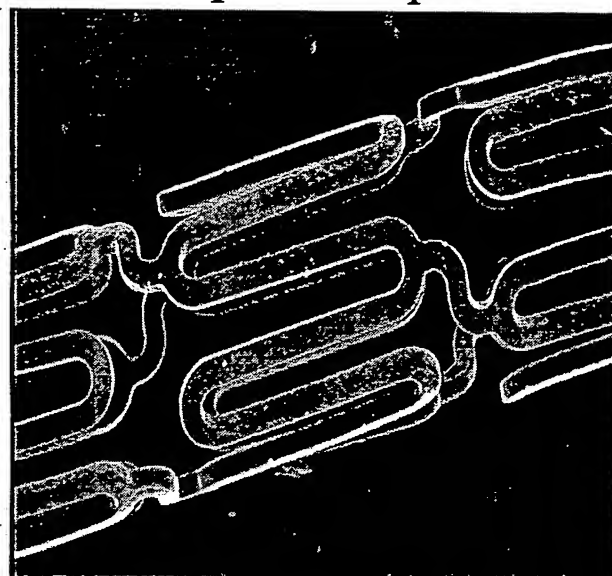


FIG. 45a

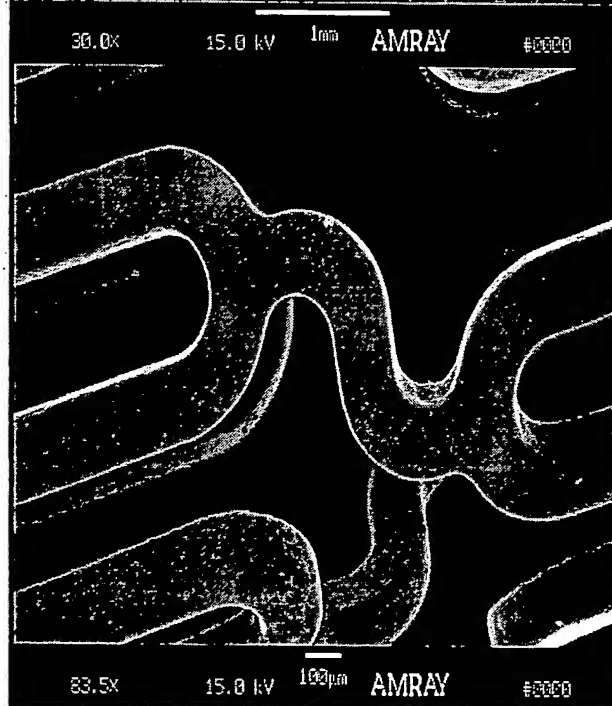


FIG. 45b

uncrimped/unexpanded

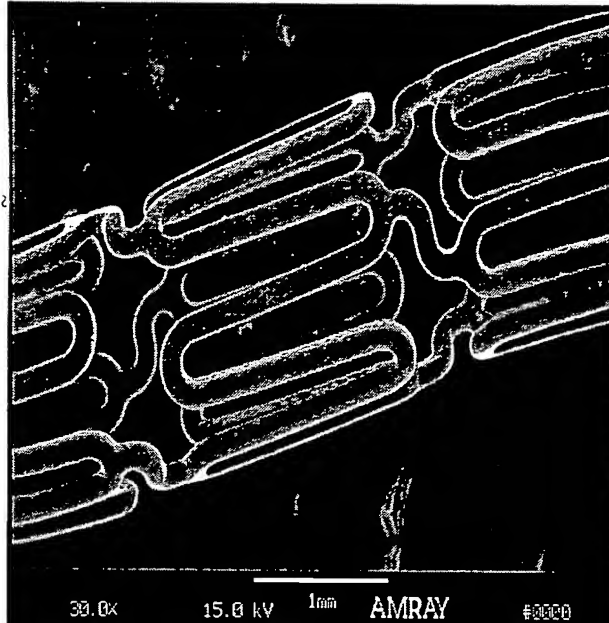


FIG. 46a

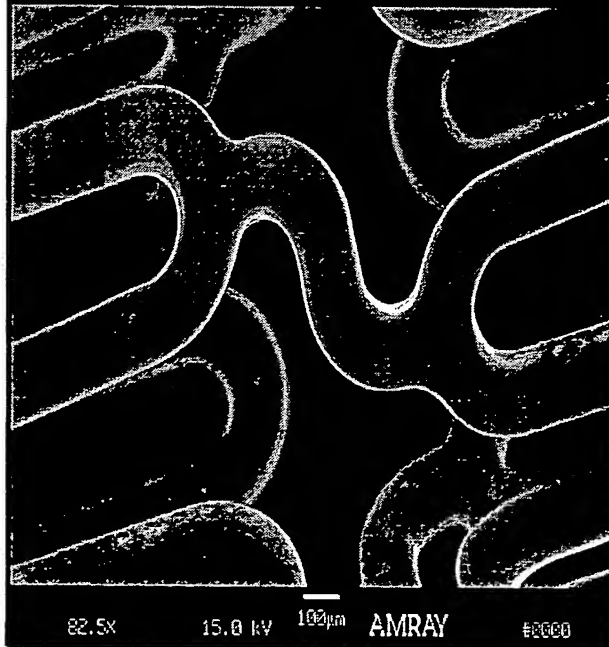


FIG. 46b